

Synthesis and conformational properties of 1,3-dimethyl-3-phenyl-1,3-azasilinane. Low temperature dynamic NMR and computational study

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Dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

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Abstract

1,3-Dimethyl-3-phenyl-1,3-azasilinane was synthesized and its conformational behavior was studied by the low temperature NMR spectroscopy and quantum chemical calculations. The compound was shown to exist as an equilibrium mixture of the Ph_{ax}Me_{eq} and Ph_{eq}Me_{ax} chair conformers with the N-methyl substituent in equatorial position. The barrier to ring inversion was also determined.

Keywords: 1,3-Dimethyl-3-phenyl-1,3-azasilinane, conformational analysis, low temperature NMR spectroscopy, quantum chemical calculations

Introduction

Azasilinanenes, and in particular 1,4-azasilinanenes, are the most studied heterocyclic organosilicon compounds.¹ This is mainly due to the fact that they are analogs of known drugs possessing specific pharmacological properties.²⁻⁸ Effective methods for their preparation as well as X-ray investigation of their molecular structure have been reported.³⁻⁸ Recently, a renewal of interest in 1,3-azasilinanenes has occurred as potential biologically active compounds.^{9,10} A distinctive feature of bioactive 1,3- and 1,4-azasilinanenes is the presence of aryl at silicon and that the biological activity proved to be dependent on the axial *or* equatorial orientation of the aryl group. The stereochemistry of the carbon analogs, geminally disubstituted 3-Me-3-Ph-piperidines has been studied by ¹H and ¹³C NMR spectroscopy, although only at room temperature.¹¹

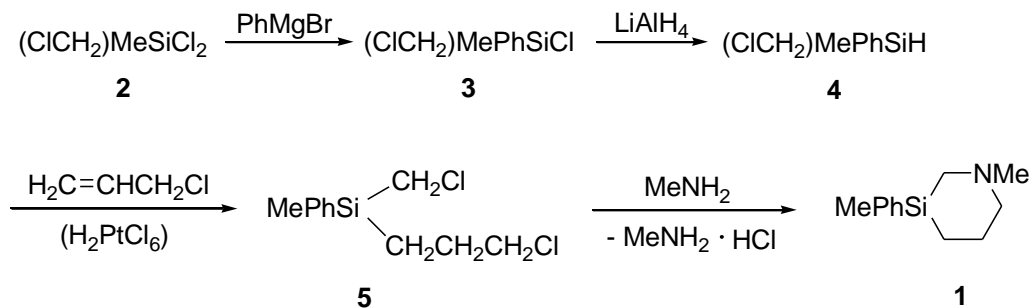
Cyclic organosilicon compounds having a Ph–Si bond are of general interest from both synthetic and theoretical point of view. Cleavage of this bond with electrophilic agents provides the possibility for preparing the corresponding sila-functionalized heterocycles such as silacyclohexanes,^{1,12} 1,3-thiasilinananes¹² and e.g. 1,3-azasilinananes.¹⁰ We also prepared 3-X-3-Me-1,3-thiasilinananes (X = H, F) from 3-Me-3-Ph-1,3-thiasilinananes¹² in order to study the conformational behavior of the latter thiasilinananes^{13,14} as well as of 3-Me-3-Ph-1,3-thiasilinanane itself.¹⁴

It is a general rule that monosubstituted cyclohexanes prefer the equatorial conformation because of unfavorable 1,3-diaxial interactions in the axial conformation.¹⁵ In the certain case of geminally disubstituted cyclohexanes, the substituent of the larger conformational energy (A value) shows a greater preference for the equatorial position. However, even the simplest representative of this class of compounds, 1-methyl-1-phenylcyclohexane, exhibits an exception from this rule:^{16,17} the Me_{eq}Ph_{ax} conformer is 0.32 kcal mol⁻¹ more stable than the Me_{ax}Ph_{eq} conformer in spite of the larger conformational energy of the phenyl group (2.87 kcal mol⁻¹)¹⁵ as compared to the methyl group (1.80 kcal mol⁻¹)¹⁵ and the stability of the Me_{eq}Ph_{ax} and Me_{ax}Ph_{eq} conformers is reversed again in favor of the latter when the two substituents are attached to silicon, rather than to carbon, as we have exemplified for 1-methyl-1-phenyl-1-silacyclohexane and 3-methyl-3-phenyl-3-thiasilinanane.¹⁴

In continuation of our systematic studies of the effect of heteroatoms on the conformational preferences of the geminally Si-Me,Ph substituted six-membered heterocycles we report in this paper the synthesis of 1,3-dimethyl-3-phenyl-1,3-azasilinanane **1** and the elucidation of its conformational behavior by low-temperature NMR spectroscopy and quantum chemical calculations.

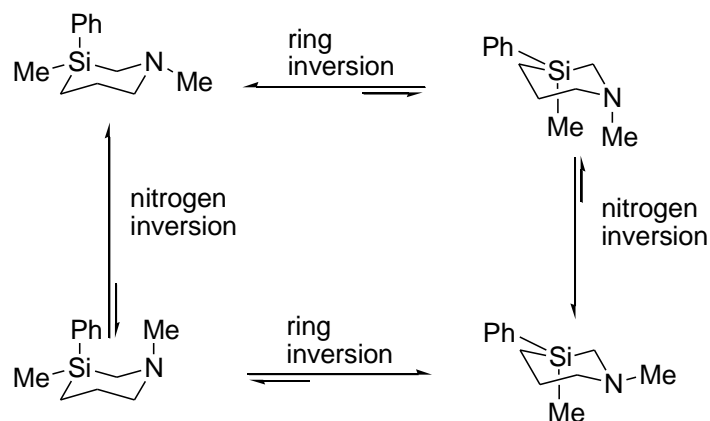
Results and Discussion

1,3-Dimethyl-3-phenyl-1,3-azasilinanane **1** was synthesized starting from (chloromethyl)methyl-dichlorosilane **2** (Scheme 1). The treatment of **2** with PhMgBr gave (chloromethyl)methyl-phenylchlorosilane **3** (50% yield), which upon the reaction with LiAlH₄ afforded the corresponding hydrosilane **4** (75% yield). Reaction of **4** with allyl chloride in the presence of Speier's catalyst resulted in the corresponding adduct **5** (11% yield), which by sequential treatment with MeNH₂ in benzene solution finally afforded the title compound **1** (57% yield).



Scheme 1

In the room temperature ^{13}C NMR spectrum each carbon atom is represented by a single line. Due to the presence of the chiral silicon center in the molecule, protons of methylene groups are diastereotopic: at 273 K, the 4- CH^A and 4- CH^B resonate separately at 0.85 and 1.00 ppm as multiplets of 8 lines each, the 5- CH_2 group exhibiting a very complex multiplet at about 2.00 ppm, the 2- CH_2 group proves to be an AB system at 2.10 and 2.15 ppm, respectively, and the 6- CH^A and 6- CH^B protons also resonate separately at 2.4 and 2.5 ppm as multiplets, the former overlapped with the NMe singlet. With lowering the temperature, all proton signals are broadened and split finally indicating that compound **1** exists as an equilibrium mixture of two conformers shown in Scheme 2. The dynamic ^1H NMR study is given in Figure 1, the resolved ^1H NMR spectrum with assignment of the signals is shown in Figure 2, the ^1H and ^{13}C signals of the aliphatic part are given in Table 1; aromatic ^1H and ^{13}C parts of the spectra are congruent.



Scheme 2

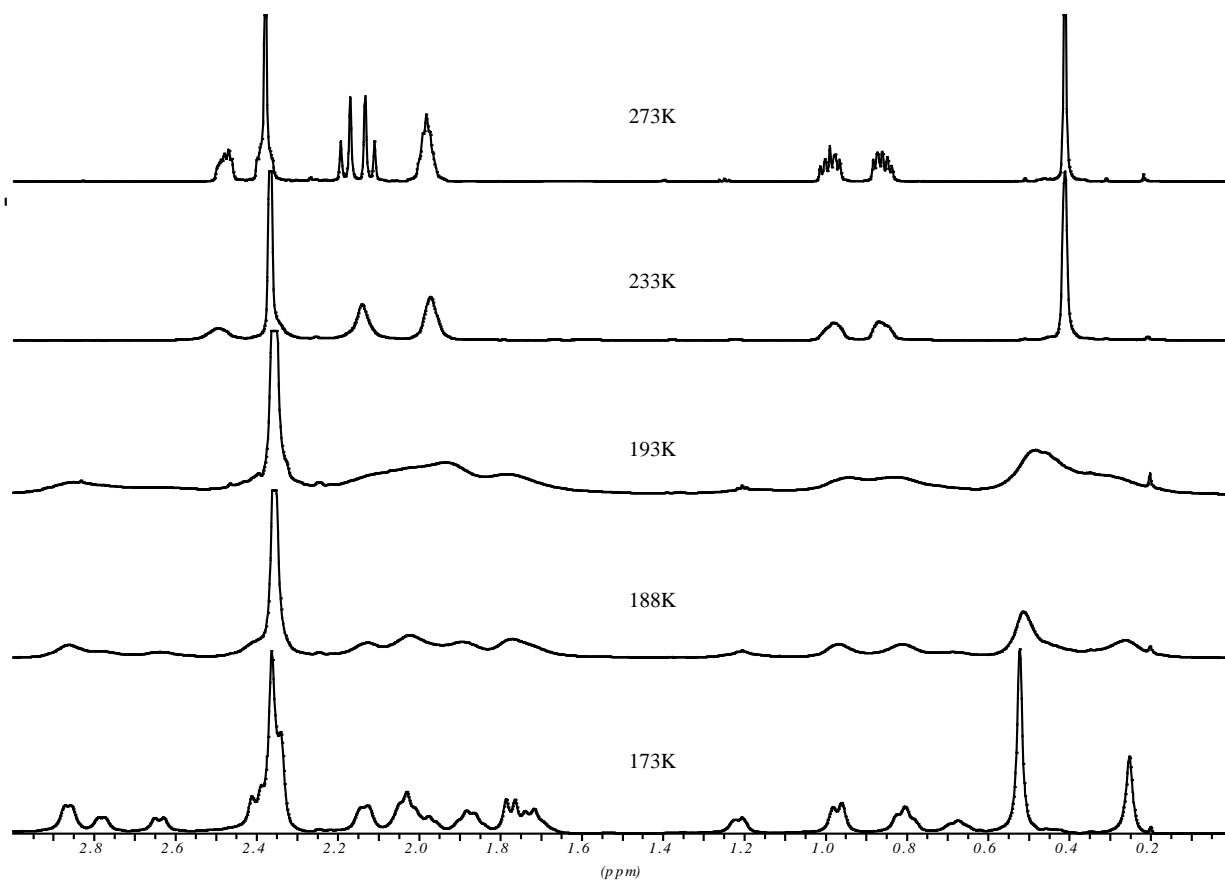


Figure 1. Variable temperature ^1H NMR spectra of 1,3-dimethyl-3-phenyl-1,3-azasilinane **1**.

Table 1. ^1H and ^{13}C NMR data for compound **1** in $\text{CD}_2\text{Cl}_2/\text{CHCl}_2\text{F}/\text{CHClF}_2$

T/K, conform.	Si–Me	$\delta(^1\text{H})/\text{ppm}$					
		MeSi	2- CH_2	4- CH_2	5- CH_2	6- CH_2	NMe
273		0.42	2.15	0.86	1.99	2.38	2.38
				0.99		2.48	
173, 1b	<i>ax</i>	0.52	1.77	0.81	1.88	2.03	
<i>major</i>	<i>eq</i>		2.40	0.97	2.13	2.86	2.36
173, 1a	<i>ax</i>		1.73	0.67	~1.70	~1.98	
<i>minor</i>	<i>eq</i>	0.25	2.64	1.21	~1.98	2.78	2.34
		$\delta(^{13}\text{C})/\text{ppm}$					
273		-4.78	48.53	10.71	25.20	60.38	52.67
173, 1b	<i>ax</i>	-7.07	47.38	9.58	24.09	59.22	51.85
<i>major</i>							
173, 1a	<i>eq</i>	-3.75	46.94	9.09	24.32	59.16	51.98
<i>minor</i>							

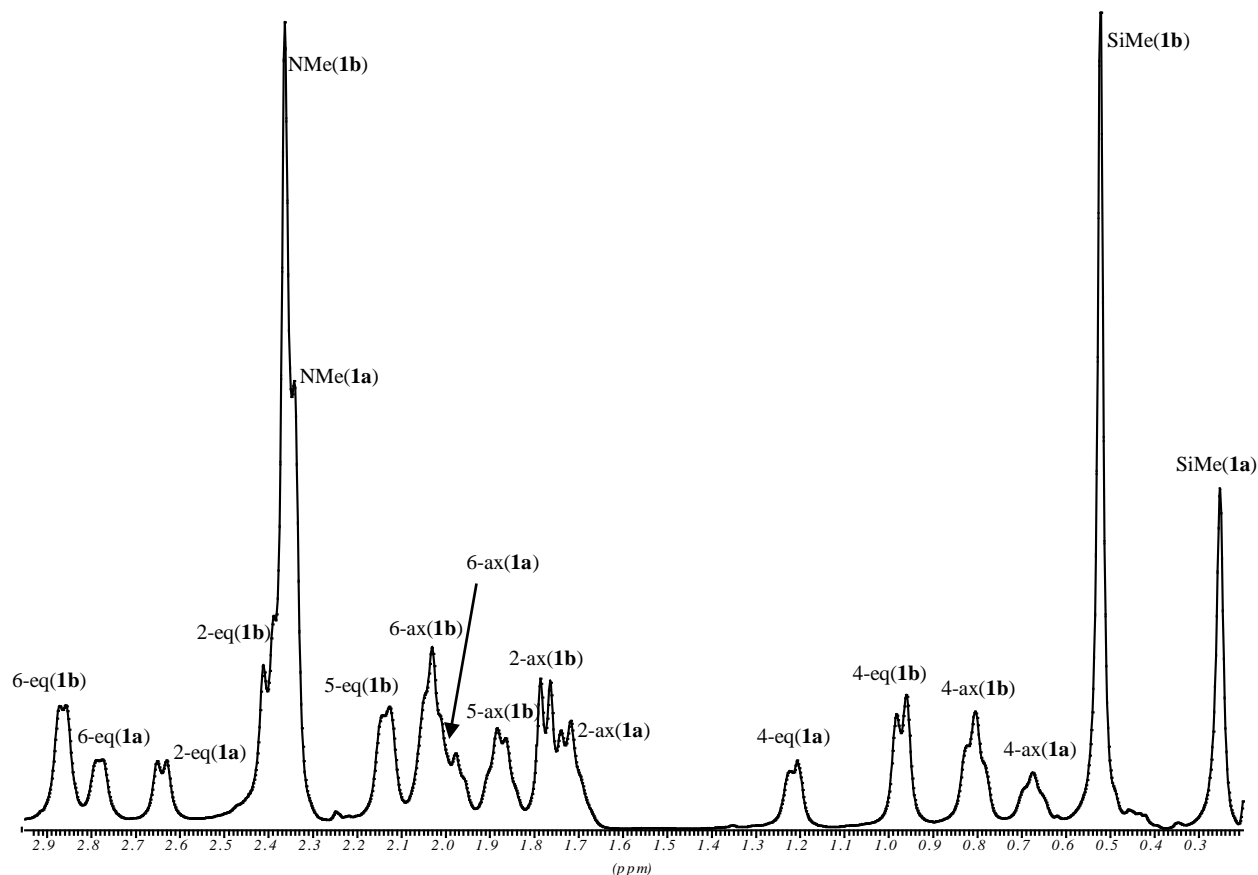


Figure 2. ^1H NMR spectrum of the frozen conformational equilibrium of 1,3-dimethyl-3-phenyl-1,3-azasilinane **1** at 173 K.

The assignment of signals in the frozen ^1H NMR spectrum (Figure 2) was made taking into account the splitting [axial protons with two (at C4 and C-6) or three large couplings (at C5), $^3\text{J}(\text{gem})$, $^3\text{J}(\text{ax},\text{ax})$] and the integral intensities of the signals, and using the HMQC and HMBC 2D NMR spectra at 143 K. The ratio of the conformers is ca. 2:1. The assignment of the proton and carbon signals to the two preferred conformers **1a** and **1b** (Figure 2, Table 1) is in agreement with criteria established for 1-methyl-1-phenylcyclohexane,¹⁶ 3,5- and 3,6-dimethyl substituted 3-arylpiperidines:¹¹ (i) equatorial H-2 and H-4 are deshielded in the $\text{Me}_{\text{eq}}\text{Ph}_{\text{ax}}$ conformer **1a** as compared to those in the $\text{Me}_{\text{ax}}\text{Ph}_{\text{eq}}$ conformer **1b**; (ii) axial H-2 and H-4 are shielded in **1a** as compared to **1b**; (iii) axial 3-Me protons are deshielded by the nitrogen lone pair in **1b** as compared to **1a**; (iv) the axial SiMe carbon atom in **1b** must resonate at higher field than the equatorial analog in **1a**. Applying these criteria, the frozen spectra in Figure 2 allow us to conclude that **1a** ($3\text{-Me}_{\text{eq}}\text{-3-Ph}_{\text{ax}}$) is the minor conformer and **1b** ($3\text{-Me}_{\text{ax}}\text{-3-Ph}_{\text{eq}}$) is the major conformer. This assignment was unequivocally proved by the 2D HMBC NMR spectrum: the methyl carbon atom of the major conformer exhibits cross peaks to C(2,4)-H(ax) while the phenyl *ipso* carbon atom of the minor conformers exhibit the corresponding cross peaks to C(2,4)-H(ax) only; cross peaks between SiMe carbon and C_{ipso} to H(2,4)*eq* protons, respectively,

are not present due to the dihedral angle dependence of the vicinal $^3J(\text{C,H})$ coupling as origin for the cross peaks.

A lower stability of the 3-Me_{eq}-3-Ph_{ax} conformer **1a** is consistent with the same order of stability earlier found by us for 1-methyl-1-phenyl-1-silacyclohexane and 3-methyl-3-phenyl-1,3-thiasilinane¹⁴ and with the larger conformational energy of the phenyl group. This order of stability is different from that for 1-methyl-1-phenylcyclohexane;¹⁷ the reasons were analyzed in detail previously.¹⁴ Possible explanation of the lower stability of **1a** vs. **1b** comes from consideration of the optimized structure of the molecule (Figure 3).

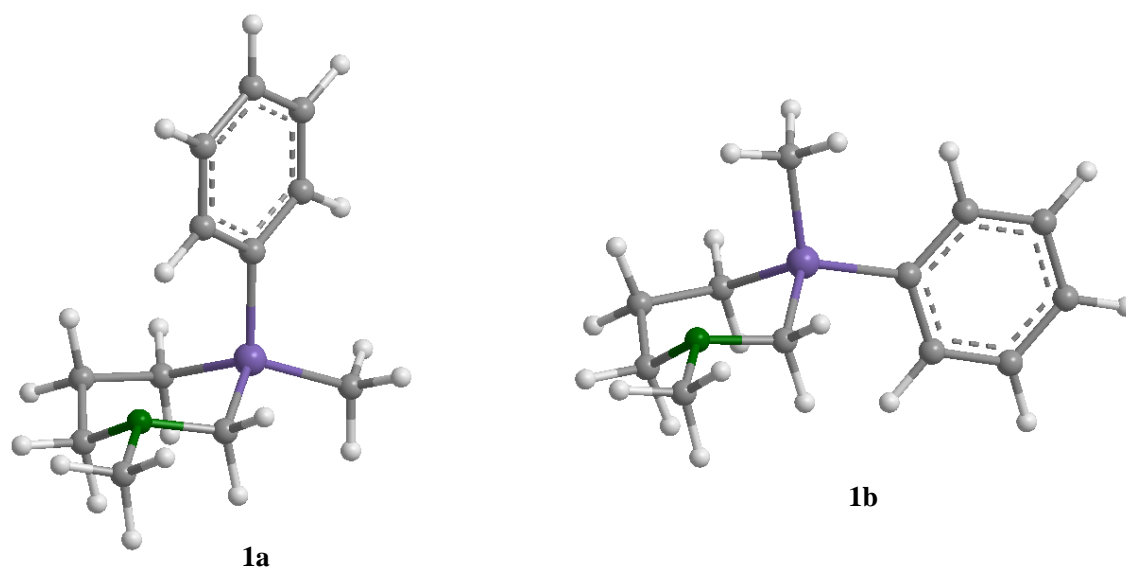


Figure 3. Optimized structure of conformers **1a** and **1b**.

In conformer **1b** the plane of the equatorial phenyl group is perpendicular to the mean plane N1–C2–C4–C6 of the 1,3-azasilinane ring system, whereas in conformer **1a** the plane of the axial phenyl group is turned about the Si–C_{ipso} bond in such a way that one of the *ortho*-protons is oriented directly to the lone pair of the nitrogen atom. This results in a reduced contact N···H_{ortho} of 2.49 Å, which is 0.21 Å shorter than the sum of the van der Waals radii (2.7 Å) and provides an additional steric destabilization of **1a** as confirmed by some shortening of the interacting C–H_{ortho} bond as compared to the corresponding *noninteracting* C–H_{ortho} bond.

The presence of only one NMe signal for each conformer is indicative of the fact that the nitrogen inversion is still fast on the NMR time scale at the temperature of our measurements.

The ratio of the conformers **1a** : **1b** of 1 : 2 in the frozen equilibrium corresponds to a free energy difference $\Delta G^{\circ} = 0.24 \text{ kcal mol}^{-1}$.

The barrier to ring inversion ΔG^{\ddagger} of 9.0 kcal mol⁻¹ was calculated from decoalescence of the SiMe protons, SiMe carbons and C-2, C-4 and C-5 signals, as shown in Table 2.

Table 2. Dynamic NMR parameters and barrier to ring inversion of 1,3-dimethyl-3-phenyl-1,3-azasilinane **1**

Decoalescing signals	T _c , K	Δν _c , Hz	k _c , s ⁻¹	ΔG _c [‡] , kcal mol ⁻¹
¹ H (SiMe)	195	160	355	9.0
¹³ C (SiMe)	203	500	1111	8.9
¹³ C (C-2)	188	61	135	9.0
¹³ C (C-4)	188	74	164	8.9
¹³ C (C-5)	186	35	78	9.1
			Mean	9.0

The mean value of the barrier is practically the same as that for the recently studied close analog of **1**, 1,3,3-trimethyl-1,3-azasilinane (9.1 kcal mol⁻¹).¹⁸ The measured barrier is lower than those in N-methylpiperidine (14.4 kcal mol⁻¹)¹⁹ or 1,3,3-trimethylpiperidine (10.8 kcal mol⁻¹),²⁰ but markedly higher than that in 1-methyl-1-phenylsilacyclohexane (5.5 – 6.0 kcal mol⁻¹).¹⁴

In order to verify the conclusions about structure and participation of the predominant conformers in the conformational equilibrium made on the basis of the NMR criteria (vide supra), we have performed quantum chemical calculations of conformers **1a** and **1b** as well as their NMe_{ax} counterparts at the MP2/6-311G(d,p) level of theory. The Me_{eq}Ph_{ax} conformer **1a** turned out to be 1.42 kcal mol⁻¹ more stable than **1b**. The gas phase free energy difference ΔG^o(298 K) = ΔG^o(**1a**) – ΔG^o(**1b**) obtained from vibrational calculations at the same level of theory is twice as low as that and equal to 0.74 kcal mol⁻¹. This result is opposite to the unequivocal experimental result obtained in freon mixture, which may be attributed to additional stabilization of **1b** in solution due to more accessible lone pair of the nitrogen atom in it (Fig. 4). Inclusion of PCM has changed slightly the calculated values but has not affected the trend discussed. Still, both the calculated and experimental values of ΔG^o are small, which is consistent with comparable amounts of the two conformers.

The corresponding NMe_{ax} conformers are 5.23 and 4.97 kcal mol⁻¹ higher in energy than **1a** and **1b**, respectively, approving the presence of only one conformer for the given configuration of the substituents at silicon.

Conclusions

1,3-Dimethyl-3-phenyl-1,3-azasilinane **1** exists as an equilibrium mixture of the two conformers with equatorial N–Me substitution and differing by the configuration of the phenyl and methyl substituents at the silicon atom, the Ph_{eq}Me_{ax} conformer **1b** being preferable. The ratio of the conformers Ph_{ax}Me_{eq} : Ph_{eq}Me_{ax} is 1 : 2, and the barrier to the silapiperidine ring inversion calculated from decoalescence of five pairs of the ¹H and ¹³C signals is 9.0 kcal mol⁻¹, which

practically coincides with the barrier in its close analog 1,3,3-trimethyl-1,3-azasilinane (9.1 kcal mol⁻¹).

Experimental Section

General. Solvents were freshly distilled from the appropriate drying agents immediately before use (diethyl ether, sodium benzophenone ketyl; benzene, CaH₂). The ¹H, ¹³C, and ²⁹Si NMR spectra were recorded on a Bruker DPX 400 spectrometer (¹H, 400.1 MHz; ¹³C, 100.6 MHz; ²⁹Si, 79.5 MHz). Chemical shifts (ppm) were determined relative to residual CHCl₃ (¹H, δ 7.27, CDCl₃), internal CDCl₃ (¹³C, δ 77.0, CDCl₃), and external TMS (²⁹Si, δ 0.00, CDCl₃). The assignment of the ¹H and ¹³C signals was made from the *j*-mod and 2D{¹H-¹³C} NMR spectra at 298K and 173K.

Low-temperature ¹H and ¹³C NMR spectra were recorded on a Bruker AV-600 (at 600 and 150 MHz, respectively). Chemical shifts were determined relative to residual internal CD₂Cl₂ (¹³C, δ 53.73) and are given in ppm downfield to TMS. Analysis and assignment of the ¹H NMR data were supported by homonuclear (COSY) and heteronuclear (HSQC ¹³C-¹H, HMBC ¹³C-¹H) 2D correlation experiments. A solvent mixture of CD₂Cl₂, CHFCl₂, and CHF₂Cl in a ratio of 1:1:3 was used for the low temperature measurements. The probe temperature was calibrated by means of a thermocouple PT 100 inserted into a dummy tube. The low temperature measurements were estimated to be accurate to ±2 K. The chemical shifts difference Δν_c, Hz was determined by extrapolation from the lowest temperatures available to T_c used to calculate k_c and the ring inversion barriers by the Eyring equation at T_c.

The HRMS ESI spectra were recorded using a Micromass Q-TOF_{micro} mass spectrometer in positive electrospray mode. All samples were injected (10 μL/min) with a Harvard syringe pump. The capillary voltage was set to 3.7 kV, with a cone voltage between 20–25 V. Elemental compositions were determined by accurate mass measurement with standard deviation < 5ppm. H₃PO₄ was used as reference compound.

Synthetic procedures

(Chloromethyl)methyldichlorosilane (**2**) was commercially available. (Chloromethyl)methylphenylchlorosilane (**3**) and (chloromethyl)methylphenylsilane (**4**) were prepared following described procedures.^{12, 21}

NMR data for compound 4. ¹H NMR (CDCl₃): δ_H 0.53 (3H, d, *J*_{HH} = 3.7 Hz, MeSi), 3.03 (1H, dd, *J*_{HH} = 13.7, 3.4 Hz, SiCH^ACl), 3.09 (1H, dd, *J*_{HH} = 13.7, 2.2 Hz, SiCH^BCl), 4.58 (1H, quint, d, *J*_{HH} = 3.6, 2.3 Hz, SiH), 7.42 (3H, m, H_{*m+p*}), 7.61 (2H, m, H_{*o*}). ¹³C NMR (CDCl₃): δ_C -7.12 (MeSi), 28.12 (SiCH₂Cl), 128.14 (C_{*m*}), 130.17 (C_{*p*}), 133.26 (C_{*o*}), 134.55 (C_{*i*}). ²⁹Si NMR (CDCl₃): δ_{Si} -14.86.

Methylphenyl(chloromethyl)(3-chloropropyl)silane (5) was prepared from **4** and allyl chloride in the presence of H₂PtCl₆•6H₂O (0.1 N solution in *i*-PrOH) by the known procedure²² in 11%

yield and purified by column chromatography on silica gel (eluent – *n*-pentane). ^1H NMR (CDCl_3): δ_{H} 0.46 (3H, s, MeSi), 1.08 (1H, dd, $J_{\text{HH}} = 11.2, 0.9$ Hz, $\text{SiCH}^{\text{A}}\text{CC}$), 1.10 (1H, d, $J_{\text{HH}} = 11.2$ Hz, $\text{SiCH}^{\text{B}}\text{CC}$), 1.87 (2H, m, SiCCH_2C), 3.01 (1H, d, $J_{\text{HH}} = 13.8$ Hz, $\text{SiCH}^{\text{A}}\text{Cl}$), 3.06 (1H, d, $J_{\text{HH}} = 13.8$ Hz, $\text{SiCH}^{\text{B}}\text{Cl}$), 3.54 (2H, t, $J_{\text{HH}} = 6.8$ Hz, CCH_2Cl) 7.43 (3H, m, H_{m+p}), 7.56 (2H, m, H_o). ^{13}C NMR (CDCl_3): δ_{C} –6.31 (SiCH_3), 10.29 (SiCH_2C), 27.16 (CCH_2C), 28.98 (SiCH_2Cl), 47.65 (CCH_2Cl), 128.15 (C_m), 129.95 (C_p), 133.93 (C_o), 134.60 (C_i). ^{29}Si NMR (CDCl_3): $\delta_{\text{Si}} -2.65$.

1,3-Dimethyl-3-phenyl-1,3-azasilinane (1). A mixture of methylphenyl(chloromethyl)(3-chloropropyl)silane **5** (5.449 g, 22 mmol), methylamine (2.469 g, 79 mmol) and benzene (20 ml) was heated in a sealed ampoule for 6 h at 160 °C. The precipitate formed was filtered off and washed with benzene. Volatile components of the organic phase were removed under reduced pressure and the oily residue was purified by column chromatography on silica gel using dichloromethane/methanol (9:1, v/v) as the eluent. The relevant fractions were combined and the solvents removed under reduced pressure to give **1** in 58% yield as a colorless viscous liquid. ^1H and ^{13}C NMR data are given in Table 1. ^{29}Si NMR (CDCl_3): $\delta_{\text{Si}} -12.53$. HRMS (ESI): $[\text{M}+\text{H}]^+$, found 206.1347. $\text{C}_{12}\text{H}_{20}\text{NSi}$ requires 206.1365.

Theoretical calculations

Optimization of geometry and vibrational calculations were performed at the MP2 level of theory with the 6-311G(d,p) basis set. Unscaled ZPE corrections were used. All calculations were performed with the Gaussian 09 computational program.²³ No restrictions on the variation of geometric parameters were imposed during the optimization procedure. For **1a** and **1b** the calculated MP2/6-311G(d,p) energies are -811.0102473 au and -811.0079776 au, respectively; ΔE is 1.42 kcal mol⁻¹ and $\Delta G^\circ(298\text{ K})$ proves to be 0.74 kcal mol⁻¹ (from vibrational calculations) in the gas phase. The solvent in PCM calculations was CHCl_3 (maximally close to the NMR experiment). PCM calculations were performed with full geometry optimization and changed $\Delta G^\circ(298\text{ K})$ only negligibly to 0.79 kcal mol⁻¹ compared with the gas phase value.

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